Adaptation after mild traumatic brain injury

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1. General Introduction

Millions of people sustain a traumatic brain injury (TBI) every year (Roozenbeek et al., 2013). The vast majority (80-90%) of this population consists of patients with mild traumatic brain injury (mTBI) (Cassidy et al. 2014). Mild traumatic brain injury is defined by a Glasgow Coma Scale (GCS) score of 13-15, loss of consciousness (LOC) for 30 minutes or less, and/or post-traumatic amnesia (PTA) lasting maximally up to 24 hours (Kayd et al. 1993). Whereas the worldwide hospital-treated incidence of mTBI is approximately 100-300/100,000, the true population-based incidence is estimated to be above 600/100,000 (Bazarian et al. 2005; Cassidy et al. 2004). Each year, around 85,000 patients with an mTBI present at emergency departments throughout The Netherlands (Hageman et al. 2010). Patients with mTBI frequently report post-traumatic complaints such as headaches, poor concentration, and fatigue, but most of them recover spontaneously within days or weeks after injury (Cassidy et al. 2014). However, nearly one in four patients will develop persistent complaints, especially within the cognitive and affective domain, which may last for months or years after the initial injury (Lundin et al. 2006; Ettenhofer & Barry 2012; Dischinger et al. 2009; Ponsford et al. 2011; Cassidy et al. 2014). These complaints are subjective in nature and are often unaccompanied by corresponding impairments on neuropsychological tests (Carroll et al. 2014; Carroll et al. 2004; Rohling et al. 2011; Dikmen et al. 2016). The cause for persistent complaints is still largely unknown and probably involves a mixture of biopsychosocial factors (Rosenbaum & Lipton 2012; Wäljas et al. 2014; Silverberg & Iverson 2011). This absence of a clear underlying reason for post-traumatic complaints makes it difficult to predict whether complaints will persist in different patients, with comparable injury characteristics.

Structural brain injury

Conventional imaging modalities rarely aid clinicians in understanding the severity of mTBI, although clinical characteristics (i.e. GCS, LOC, PTA) indicate that patients with mTBI have indeed sustained impacts to their brains. In most cases, computed tomography (CT) performed in the acute clinical setting reveals no abnormalities, which is referred to as "uncomplicated mTBI" (Bazarian et al. 2006; Iverson et al. 2000). Furthermore, irrespective of whether or not the CT scan at admission shows abnormalities, it has been demonstrated that CT characteristics are poor predictors of self-reported complaints at follow-up or of overall outcomes after mTBI (Jacobs

et al. 2010; Lannsjö et al. 2013). One explanation could be related to the presence or absence of traumatic axonal injury, which is difficult to determine with CT and appears to be more closely related to clinical outcome after TBI compared to focal brain lesions (e.g. contusions) (Sharp & Ham 2011). Magnetic resonance imaging (MRI) has been shown to detect more traumatic axonal injury than CT in patients with mTBI, which is due to the increased sensitivity of T2*-gradient echo (T2*-GRE) and susceptibility weighted imaging (SWI) sequences for detection of microhemorrhagic lesions (Metting et al. 2007; Lee et al. 2008; Yuh et al. 2013; Huang et al. 2015; Chastain et al. 2009; Geurts et al. 2012). Therefore, MRI scans are routinely performed in cases with persistent complaints which interfere with daily functioning. However, most patients with mTBI who have normal CT scans on admission will also have normal MRI scans on follow-up; only the presence of four or more hemorrhagic axonal lesions after mTBI is significantly predictive of poorer outcome (Yuh et al. 2013; Huang et al. 2015). Additionally, studies so far have shown that patients with and without MRI abnormalities do not differ regarding the number of post-traumatic complaints (Hughes et al. 2004; Hofman et al. 2001), although these studies did not use SWI. Altogether, current research may call into question the use of conventional MRI during mTBI follow-up.

Interestingly, recent diffusion tensor imaging (DTI) studies have also shown that microstructural injury to white matter tracts may not be causative in the development of post-traumatic complaints (Lange et al. 2015; Wäljas et al. 2014). Furthermore, one recent DTI study even demonstrated that there were no differences between patients in the acute phase after mTBI and healthy controls, regardless of complaints (Ilvesmaki et al. 2014). Aforementioned studies have focused on group differences in diffusion parameters within certain brain regions; however, the relationship with structural networks (i.e. connectomes) remains unclear. Therefore, it is worthwhile to apply newer analysis techniques, such as graph theory, to study the integrity of the structural connectome in patients with mTBI. This may also enable us to capture subtle differences between patients and controls, and between patients with and without post-traumatic complaints who would have otherwise remain unnoticed.

Adaptation and the prefrontal cortex

The aforementioned studies emphasize the need to investigate brain function in mTBI from a non-injury perspective. Brain injury can be regarded as a stressful life event which challenges the capacity to deal with the consequences of such an event, i.e. psychological adaptation. The development of persistent post-traumatic complaints is likely to result from difficulties adapting to the presence of acute complaints and changes in daily life in the first weeks to months after injury. These adaptive deficits seem to be related to individual personality characteristics and coping styles (Wood

2004; Anson & Ponsford 2006; Silverberg et al. 2013).

An important aspect of adaptation is mental flexibility, which is reflected by the ability to adequately shift between internally and externally directed mental processes, for example during cognitive performance (Tops et al. 2014; Menon & Uddin 2010). Another important aspect is the ability to regulate negative emotions and stress (Ochsner & Gross 2005). Feelings of anxiety and depression are correlated with post-traumatic complaints; this indicates that emotion regulation plays an important role in the recovery from mTBI (Silverberg & Iverson 2011; Stulemeijer et al. 2007; van der Horn et al. 2013). The brain's prefrontal cortex is an essential area for adaptive behavior, because cognitive and emotional processes coalesce within this region (Cole et al. 2014; Tops et al. 2014; Frank et al. 2014; Ochsner & Gross 2005; Ochsner et al. 2012). Hence, it is plausible that premorbid prefrontal network function is associated with adaptive deficits and the persistence of complaints after mTBI. Furthermore, due to its location at the anterior part of the cranium and the anterior cranial fossa's irregular surface, the prefrontal cortex is particularly vulnerable to traumatic brain injury (Bigler 2007; McAllister 2011). Thus, if structural brain injury contributes to network dysfunction underlying adaptive deficits after mTBI, it most likely involves injury to the prefrontal cortex.

With functional magnetic resonance imaging (fMRI), it is possible to measure brain network function during cognitive paradigms and resting conditions. Furthermore, it allows the relationship of network function to behavioral and clinical measures to be assessed. Therefore, the application of fMRI may lead to valuable insights into the role of prefrontal brain networks in adaptation after mTBI. Whereas a working memory paradigm provides information about activation and deactivation of brain networks during externally focused mental processes, resting-state fMRI informs us about the intrinsic functional architecture of the brain. Among other things, studies so far have shown hyperactivation of prefrontal brain areas during performance of working memory tasks in patients with mTBI. This finding could be interpreted as a neural compensation mechanism, which may lead to cognitive complaints (Bryer et al. 2013; McAllister et al. 1999). Furthermore, resting-state fMRI studies have demonstrated that post-traumatic complaints in mTBI likely originate from an inadequate balance between medial (e.g. default mode network) and lateral (e.g. executive networks) prefrontal brain networks underlying internally and externally directed mental processes, respectively (Mayer et al. 2011; Sours et al. 2013). However, there is limited knowledge of how these brain networks are involved in emotion regulation after mTBI.

The UPFRONT study

The UPFRONT study is a Dutch multi-center prospective cohort study aimed at early identification and treatment of adaptive deficits in patients with mTBI. The

main research goal is to determine which patients are at risk for developing persistent complaints, and to define the role of prefrontal brain networks. The study consists of three sub-projects: (1) A longitudinal follow-up study in order to determine the influence of early adaptive deficits on outcome of patients with mTBI; (2) A psychological intervention study on the effectiveness of cognitive behavioral therapy versus telephone counseling in patients with a high number of self-reported post-traumatic complaints early after mTBI; and lastly, (3) A structural and functional neuroimaging study on the relationship between brain networks, adaptive deficits, and emotion regulation in patients with mTBI (the subject of this dissertation). Taken together, these projects cover a wide range of biopsychosocial confounders of outcomes after mTBI, and the combined efforts of these projects has great potential to enhance our understanding of the pathophysiology of post-traumatic sequelae.

Outline of this dissertation

The general objective of this dissertation is to investigate structural and functional brain networks in patients with uncomplicated mTBI. We are particularly interested in the role of the prefrontal cortex in the development of (persistent) post-traumatic complaints and the relationship with emotional distress. In **Chapter 2**, we present a comprehensive review of the current literature on brain networks in mTBI. In particular, the major functional brain networks for emotion regulation and adaptation in patients with and without mTBI as well as healthy subjects, are outlined. In the first experimental chapter of this dissertation (**Chapter 3**), we aim to determine the clinical relevance of traumatic microhemorrhagic injury as assessed by conventional MRI in patients with mTBI. This is done by examining the association between microhemorrhaging on T2*-GRE and SWI, and post-traumatic complaints in the subacute phase after injury. In **Chapter 4**, we use diffusion MRI to evaluate axonal integrity and possible traumatic axonal injury in the same study sample. More specifically, the structural connectome is examined with graph analysis to explore the relationships between structural network integrity, complaints, and neuropsychological outcome after mTBI. To gain more insight into how functional brain networks are related to cognitive complaints after mTBI, in **Chapter 5** we use a working memory fMRI paradigm to study differences between patients with and without complaints in the subacute post-injury phase, and healthy controls. Since emotion regulation appears to play a pivotal role in the development and persistence of post-traumatic complaints after mTBI, in **Chapter 6** we use resting-state fMRI to explore the relationship between intrinsic functional network connectivity, anxiety, depression, and post-traumatic complaints. Subsequently, we take a graph theoretical approach to assess global and local properties of intrinsic functional networks after mTBI in further detail (**Chapter 7**). In the last experimental chapter, intrinsic functional network connectivity is investigated from a longitudinal perspective in

patients with complaints who were included in an early psychological intervention study (UPFRONT sub-project 2), in addition to patients without complaints after mTBI (**Chapter 8**). This dissertation ends with a general discussion of our results and future perspectives (**Chapter 9**).